REMARKS

Claim 1-22 are currently pending. Claims 1-17 and 19-22 are withdrawn from consideration as being drawn to non-elected inventions. Claim 18 has been amended to better clarify what Applicants believe to be the invention. Support for the amendment to claim 18 can be found throughout the specification, but particularly on page 8, lines 29-32, through to page 9, lines 1-8; on page 20, lines 10-16; on page 42, line 32 to page 43, lines 1-8 and in original claim 15. No issue of new matter is believed to be introduced by this amendment. Accordingly, claim 18 is currently under consideration.

Colored Drawings

The Examiner has noted that if Applicants wish to use the color drawings originally submitted with the current application, Applicants must petition for acceptance of such drawings, and that the petition must be accompanied with payment of the appropriate fee as set forth in 37 CFR 1.17(h), three sets of colored drawings and an amendment to the first paragraph of the Brief Description of the Drawings section of the specification noting the inclusion of such colored drawings in the application. Applicants include herewith a petition for acceptance of such colored drawings pursuant to 37 C.F.R. §§ 1.84 (a)(2) and (b)(2), an amendment to the Brief Description of the Drawings section in the specification, along with submission of three sets of colored drawings, and the appropriate fee as set forth in 37 C.F.R. 1.17(h).

Objections Based on Informalities

The Examiner has objected to the disclosure for the following informalities.

In particular, the Examiner alleges that the Sequence Listing fails to meet the requirements of 37 CFR 1.821-1.825 because Figure 1 contains sequences without SEQ ID numbers. Applicants have amended Figure 1 to include the numerical sequence identifiers (SEQ ID NOs: 8-33). Furthermore, since Figure 1 is one of the drawings submitted in color to better point out particular aspects of the invention, this change has been incorporated into the text of the colored drawing, which is submitted herewith. In addition, a Substitute Sequence Listing is submitted herewith in compliance with 37 CFR 1.821-1.825 to be inserted into the instant application to replace the Sequence Listing submitted on September 24, 2002. Applicants request favorable entry of the amendment and Substitute Sequence Listing and respectfully request withdrawal of this objection.

The Examiner has also objected to claim 18 for the following informalities. In claim 18, "comprising: comprising:" should be changed to "comprising:". Furthermore "computer modeling;;" should be changed to "computer modeling;". These corrections have been made and can be found in the "Amendments to the Claims" section. Accordingly, Applicants respectfully request withdrawal of this objection.

Rejections under 35 U.S.C. §112, second paragraph

The Examiner has rejected claim 18 under 35 U.S.C. §112, second paragraph as being indefinite. Applicants have amended the claim to better clarify what they believe to be the invention. Support for the amendment to claim 18 can be found throughout the specification, but particularly on page 8, lines 29-32, through to page 9, lines 1-8; on page 20, lines 10-16; on page 42, line 32 to page 43, lines 1-8 and in original claim 15.

The Examiner alleges that the claim is indefinite because of the following phrases:

The recitation of "using the three-dimensional structure" is vague because "using" is not a positive process step. Applicants have deleted this phrase from the preamble as being redundant and unnecessary, since step a) of the claim recites similar language, but without the term "using".

The recitation of "potential compound" is vague because the instant application does not distinguish between a potential compound and a non-potential compound. While Applicants respectfully traverse the Examiner's rejection, since the definition for potential compound is clearly found on page 20, lines 10-16, Applicants have amended the claim to recite "test compound", support for which may also be found on page 20, lines 10-16.

The recitation of "computer modeling" is vague because the term is not defined in the application and there is no recognized meaning for the term. Thus, the metes and bounds of the claims are not clear. Applicants respectfully traverse the rejection and assert that the term is well known in the art and in support of such, Applicants have provided specific references that attest to this fact, which are included for the Examiner's convenience as Exhibit A through Exhibit D. One particular reference (Exhibit A) entitled "Biocomputing and Drug Design" (http://www.techfak.uni-bielefeld.de/bcd/ForAll/Introd/drugdesign.html) presents a clear description as to how computers may help to optimize the pharmacologic profile of drugs by guiding the synthesis of new or better compounds. This is accomplished by analyzing the interactions between the drug and its receptor site to "design" molecules that give an optimal fit. A second reference (Exhibit B) is a paper by Martin Norin et al. (Protein

Science (1994) Vol. 3, pages 1493-1503), whereby the authors identified the substrate binding sites of the triacyl glyceride lipases from *Rhizomucor miehei, Humicola lanuginose* and *Candida rugosa* by means of computer modeling methods. Exhibit C is an abstract of a paper by Zhang et al. (Sci China C Life Sci (2004), Vol. 47(3): 279-286) whereby the authors identified the binding epitope of a monoclonal antibody Z12 against human TNF- alpha using computer modeling techniques. Exhibit D is yet another abstract from a paper by North et al. (Proteins (1994) Vol. 20(2): 174-184), whereby the authors studied the coiled-coil rod domain structures present in keratin and other intermediate filament molecules. All of these references confirm that the term computer modeling is well known in the art.

The recitation of "using rational drug design" is vague because "using" is not a positive step process. Applicants respectfully traverse the Examiner's rejection and have amended the claim to recite "by" rather than '"using".

Furthermore, the Examiner alleges that the term "rational" is incomplete because the instant application does not distinguish between rational drug design and irrational drug design. The Examiner alleges that "rational drug design" has no art recognized meaning. Applicants respectfully traverse the Examiner's rejection and have provided a number of references in support of the fact that the term is well known and used by those skilled in the art. In particular, one reference entitled "Rational Drug Design" (Exhibit E) (http://www.wellcome.ac.uk/en/genome/tacklingdisease/hg09b002.html) discusses how the pharmaceutical industry uses rational drug design computer programs as a more focused approach and uses information about the structure of a receptor and its ligands to identify or create candidate drugs, similar to the work presented in the present application. In fact, this article notes that the first drug to be identified this way was Relenza, which is used to treat influenza. Furthermore, the article also notes that many drugs developed to treat HIV infections are designed to interact with the viral protease, the enzyme that splits up the viral proteins and allows them to assemble properly. And yet further, the article refers to the fact that Viagra was identified using this approach. That is, the drug was designed to resemble cGMP, a ligand that binds to an enzyme called phosphodiesterase. Furthermore, Exhibit F is a printout from the internet (http://www.chipsbooks.com/rational.htm) which illustrates that an entire book entitled "Rational Drug Design" has been written about this topic, and enclosed as Exhibit F is a copy of the book cover from this book edited by Donald G. Truhlar et al. Exhibit G is a reference regarding a workshop held on April 7-April 11, 1997 devoted to rational drug design. And yet further, Exhibit H is a printout of the term "rational drug

design" as illustrated in a glossary of terms from the Society for Life Science Professionals (http://www.ispe.org/glossary/definitionbyterm,cfm?term=Rational%20Drug%20Design). Applicants assert that based on the foregoing references supplied as Exhibits A through H, the terms "computer modeling" and "rational drug design" are art recognized terms. Withdrawal of this rejection is respectfully requested.

The Examiner further alleges that the recitation of "decrease in the binding affinity" is incomplete because the claim does not specifically recite that a decrease in SNT-FGFR binding is a comparison between binding in the presence of a particular compound and in the absence of a particular compound. While Applicants respectfully traverse the Examiner's rejection, claim 18 has been amended to recite in step d): "measuring the binding of the SNT or the SNT fragment with FGFR or the FGFR fragment; wherein a test compound is identified as a compound that inhibits the formation of the SNT/FGFR complex when there is a decrease in the binding of the SNT or the SNT fragment with FGFR or the FGFR fragment in the presence but not the absence of the test compound."

In light of the foregoing, withdrawal of the rejections under 35 U.S.C. 112, second paragraph is respectfully requested.

Rejections under 35 U.S.C. §103(a)

The Examiner has rejected claim 18 under 35 U.S.C. §103(a) as being unpatentable over Xu et al. (J. Biol. Chem. 273: 17987 (1998) in view of Applicants' admitted state of the prior art. In particular, the Examiner alleges that Xu et al. teach that the SNT PTB binding domain of FGFR is amino acids 401-434. Additionally, Xu et al. demonstrates that FGFR-1/SNT interaction is needed for receptor induced SNT tyrosine phosphorylation. Further, the Examiner alleges that since Applicants utilize computer modeling and 3-dimensional determination of polypeptides, it would have been obvious to one skilled in the art to create a 3-D model of the SNT PTB binding domain of FGFR-1 and SNT PTB in order to inhibit formation of the complex utilizing the activity as disclosed by XU et al. Furthermore, the Examiner alleges that it would have been obvious to "trim down" the FGFR-1 residues to the exact sequence of SEQ ID NO: 3 by step wise deletion of the amino acids from 401-434 to that described in the instant application. Applicants respectfully traverse the Examiner's rejection for the following reasons.

The Examiner has the initial burden of establishing a *prima facie* case of obviousness. A finding of obviousness under § 103 requires a determination of the scope and

content of the prior art, the differences between the claimed invention and the prior art, the level of ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Graham v. Deere, 383 US 1 (1966). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion that the combination be made. In re Stencel, 828 F2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987). Furthermore, there must be a reasonable expectation of success for a rejection under § 103 to be proper.

The invention as claimed. The claims as amended are drawn to a method of identifying a compound that inhibits the formation of a SNT/FGFR complex. In particular, the steps comprise obtaining a set of atomic coordinates defining the three-dimensional structure of a SNT/FGFR complex consisting of a fragment of SNT consisting of amino acid residues 11-140 of SEQ ID NO:1 and a 22 amino acid fragment of FGFR consisting of SEQ ID NO:3; selecting a test compound that binds to the PTB domain of SNT; wherein said selecting is performed by rational drug design with the set of atomic coordinates obtained from step (a), and is performed in conjunction with computer modeling; contacting the test compound with an SNT or an SNT fragment, and FGFR or an FGFR fragment under conditions in which the SNT/FGFR complex can form in the absence of the test compound; and measuring the binding of the SNT or the SNT fragment with FGFR or the FGFR fragment; wherein a test compound is identified as a compound that inhibits the formation of the SNT/FGFR complex when there is a decrease in the binding of the SNT or the SNT fragment with FGFR or the FGFR fragment in the presence but not the absence of the test compound.

The Xu et al. reference as a whole. Xu et al. teach that the SNT PTB binding domain of FGFR is amino acids 401-434. Additionally, Xu et al. demonstrate that FGFR-1/SNT interaction is needed for receptor induced SNT tyrosine phosphorylation. Moreover, as the Examiner has pointed out, Xu et al describe on page 17990 in the first paragraph that **residues 401-434 of FGFR are both necessary and sufficient for interaction with SNT PTB domains.**

Xu et al. do not teach or suggest the binding coordinates defining the three-dimensional structure of a SNT/FGFR complex consisting of residues 11-140 of SEQ ID NO:

1 and the smaller fragment of the FGFR (SEQ ID NO: 3) nor do they suggest their use for identifying compounds that inhibit the formation of the complex.

The analysis under § 103(a).

A. The Examiner has not set forth a proper *prima facie* case of obviousness.

Xu et al. do not teach or suggest determination of the binding coordinates that define the three dimensional structure of the SNT/FGFR complex for use in identification of inhibitors of complex formation. Moreover, Xu et al. do not consider that a smaller fragment of FGFR (the 22 amino acid residues of SEQ ID NO: 3) could be useful for screening for such compounds. In fact, Xu et al. state exactly that in the cited reference. That is, Xu et al distinctly state that residues 401-434 are **necessary** for interaction with SNT PTB domains. Thus, there is no teaching or suggestion and no motivation to combine the teachings of Xu et al. with the teachings of the present invention since Xu et al. specifically state **that the larger fragment is necessary** for the interaction to occur. A skilled artisan, upon reading the Xu et al. reference, would not be motivated to combine this reference with the teachings of the present application since there would appear to be no reasonable expectation for success. Moreover, since the interaction of the smaller fragment of FGFR (SEQ ID NO: 3 of the present application) with the SNT PTB domain was unknown at the time of the Xu et al. reference, it was not possible to predict the use of this smaller fragment and molecular modeling for drug screening until the time of the present invention.

Moreover, it was not until Applicants' present invention that the identity and sequence of the smaller fragment of FGFR (SEQ ID NO: 3) was identified as being **sufficient** to use for drug screening.

B. Xu et al. teach away from the present invention.

Applicants assert that the statement of Xu et al. on page 17990 teaches that only the larger sequence, ie. 401-434 of FGFR is both **necessary and sufficient** for interaction with the SNT PTB domains, and therefore there would be no motivation or expectation for success by use of the smaller fragment of SEQ ID NO: 3 of the present application to work.

Thus, the connection between the work done by Xu et al. would not have been obvious in view of the teachings of the present application since Xu et al clearly teach away from the present invention by reciting that **residues 401-434 of FGFR are necessary and sufficient for the interaction** to occur. There would be no motivation or suggestion to

combine the teachings of Xu et al. with the state of the art as taught by the present application since one skilled in the art would not feel that there would be a reasonable expectation for success with any fragment smaller than residues 401-434 of FGFR. Applicants' discovery of the interaction of FGFR fragment of SEQ ID NO: 3 and SNT PTB using the methods described in the present application was not carried out earlier by Xu et al, due to failure to recognize and appreciate that a smaller sequence of the FGFR (SEQ ID NO: 3) could be **sufficient** for the interaction to occur.

In light of the foregoing claim amendments and arguments, Applicants respectfully request withdrawal of the rejection.

Fees

A check in the amount of $130.00 is enclosed in accordance with 37 C.F.R §1.17 (h) as payment for the petition for acceptance of colored drawings. No other fees are believe to be necessitated by the foregoing response. However, if this is in error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment, or credit any overages.

Conclusion

Applicants believe that the foregoing amendments to the claims place the application in condition for allowance. Withdrawal of the rejections is respectfully requested. If a discussion with the undersigned will be of assistance in resolving any remaining issues, the Examiner is invited to telephone the undersigned at (201) 487-5800, ext. 118, to effect a resolution.

Respectfully submitted,

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Attachments: Exhibits A-H; Substitute Sequence Listing and Statement; Three sets of colored drawings; Petition for acceptance of colored drawings.